Journal of Cancer Research and Practice 3 (2016) 49–53

Contents lists available at ScienceDirect

Journal of Cancer Research and Practice

journal homepage: http://www.journals.elsevier.com/journal-of-cancer-research-and-practice

Case report

Metastatic carcinoma of the urinary bladder in a 67-year-old female with underlying triple primary cancers

Chia-Yen Hung [a], Shir-Hwa Ueng [b], Yung-Chang Lin [a], Wen-Chi Chou [a, *]

[a] Division of Hematology and Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou and Chang Gung University School of Medicine, Taoyuan, Taiwan

[b] Department of Pathology, Chang Gung Memorial Hospital at Linkou and Chang Gung University School of Medicine, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Received 7 July 2015
Accepted 3 September 2015
Available online 21 March 2016

Keywords:
Multiple primary cancers
Signet ring cell carcinoma
Invasive lobular carcinoma
Metastatic urinary bladder cancer

ABSTRACT

Due to progressive ageing of our population and increasing cancer incidence rates, more and more patients are presenting with multiple primary cancers. Here we describe a case of metastatic carcinoma involving the urinary bladder with underlying triple primary adenocarcinoma in a female adult.

A 67-year-old Taiwanese female presented to our institution in November 1997 with gastric signet ring cell carcinoma, pT2N0M0, status post subtotal gastrectomy. In February 2003 she was diagnosed with left breast invasive lobular carcinoma status post modified radical mastectomy, pT2N2M0. Further examination in January 2005 revealed proximal transverse colon cancer, Dukes' C2, with status post right hemicolectomy. She achieved disease-free status from all three malignancies after surgical resection and adjuvant chemotherapy for breast and colon cancers sequentially. In November 2011, she complained about sudden onset of gross hematuria for several days. Diagnostic cystoscopy showed a mass lesion over her urinary bladder. Cystoscope-assisted biopsy showed metastatic poorly differentiated adenocarcinoma with signet ring appearance. Herein we have discussed the pathologic role in the diagnosis of metastatic tumor involving a patient with multiple primary cancers. We also explored the epidemiologic risk and potential causal mechanism of patients with multiple primary cancers.

1. Introduction

The term “Multiple primary neoplasm (MPN)” was first documented by Billroth et al in 1889. Recently, a trend towards an increase prevalence rate of MPN was noted and probably due to improved treatment results and prognosis of various cancers.[1] Additionally, early tumor detection through an elevated frequency of cancer screening also may impact this increased diagnosis of MPN.[1] Based on the Surveillance Epidemiology and End Results (SEER) data between 1973 and 2000, cancer survivors had a 14% higher risk of developing a new malignancy, and an heightened absolute risk of 21 cancer cases per 10,000 person-years than the general population.[1]

MPN has been identified in those cases harboring multiple tumors that meet the criteria by Warren and Gates as follows: 1) Each neoplasm must be malignant arising from histological evaluation; 2) Each neoplasm must be anatomically separate and distinct. If the intervening mucosa demonstrates dysplasia, it must be considered as a multicentric primary lesion and not as two separate neoplasms; and 3) The possibility that the second neoplasm represents a metastasis should be excluded.[2] However, the differentiation of second primary cancer from metastasis is still arguable mainly under the assistance of distance, diagnosis time difference or even molecular analysis of different tumors.[3–5]

Cases involving more than two primary malignant neoplasms are very rare. In this report, we present the case of a female patient with metastatic carcinoma of the urinary bladder from metachronous triple primary malignant neoplasms of: 1) the stomach first, 2) then the left breast, and then 3) the transverse colon, which is an extremely rare combination.

* Corresponding author. Division of Hematology and Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou and Chang Gung University School of Medicine, No. 5, Fuxing Road, Guishin Town, Taoyuan 333, Taiwan.

E-mail address: wenchi3992@yahoo.com.tw (W.-C. Chou).

Peer review under responsibility of The Chinese Oncology Society.

http://dx.doi.org/10.1016/j.jcrpr.2015.09.002

2. Case report

A 67-year-old female patient was diagnosed with gastric signet ring cell carcinoma, pT2N0M0, status post subtotal gastrectomy in November 1997. Then she was diagnosed with a second primary malignancy, left breast cancer, invasive lobular carcinoma, pT2N2M0, estrogen receptor (ER) 2+, progesterone receptor (PR) 2+, status post left modified radical mastectomy in February 2003, followed by adjuvant chemotherapy with CEF regimen (cyclophosphamide, epirubicin and 5-fluouracil) and adjuvant hormone therapy with tamoxifen for five years. In January 2005, the patient was diagnosed with a third primary neoplasm, proximal transverse colon cancer, moderately differentiated adenocarcinoma, Dukes' stage C2, and underwent status post right hemicolectomy in November 2005; this was followed by adjuvant chemotherapy with mFOLFOX-6 regimen (5-fluouracil, leucovorin and oxaliplatin). However, after the first cycle of mFOLFOX-6 regimen, she switched to capecitabine due to an allergic reaction to oxaliplatin.

The patient then achieved disease-free status as noted in a series of routine image studies during regular follow-up at our oncology clinic. In November 2011, she presented due to hematuria for several days. Diagnostic cystoscopy showed a mass lesion on the urinary bladder. Whole body computed tomography (CT) scan revealed an isolated 2.6 × 2 cm tumor in the right posterior lateral wall of the urinary bladder (Fig. 1). Cystoscope-assisted biopsy showed a poorly differentiated adenocarcinoma with signet ring appearance arising from the submucosa of the urinary bladder. A metastatic cancer rather than primary urinary bladder cancer was impressed according to microscopic morphology of tumor and intact mucosa of urinary bladder. Immunohistochemical (IHC) profiles of the urinary bladder tumor revealed the expression pattern as CK7+, CK20+, CDX2−, ER− and scattered expression of PR. Colon origin was excluded due to different morphologic appearance and IHC profiles comparing to previous colon cancer specimen, which had strong CDX-2 expression. Recurrent breast cancer was found to be unlikely due to different ER and PR expression patterns compared to the primary breast cancer.

Under the preliminary diagnosis of recurrent gastric cancer with solitary urinary bladder metastasis, she received palliative chemotherapy with weekly high-dose 5-fluorouracil followed by radiotherapy (5040 centi-Gray divided into 28 fractions) for the isolated metastatic tumor. Complete tumor response was achieved and there was no evidence of residual tumor by subsequent tumor marker (Fig. 2) and imaging follow-up. The patient experienced abdominal distension and bilateral leg edema in September 2013. A subsequent CT scan showed multiple metastatic lymph nodes over para-aortic areas (Fig. 3). Palliative chemotherapy with docetaxel + cisplatin regimen was administered as a second line palliative chemotherapy for recurrent gastric cancer with lymph node metastasis based on previous urinary bladder tumor scenario. Nevertheless, in May 2014, she complained of progressive enlarged left neck lymph nodes within half a year. Images showed the tumor had progressed with multiple lymph nodes metastases mainly involving left supra-clavicle, and mediastinum areas. The patient received neck lymph node biopsy because of the bizarre growth rate of her neck lymph node, and the pathologic report confirmed metastatic carcinoma. However, the microscopic appearance and IHC profiles of neck lymph node tumor were distinct to the urinary bladder tumor. A complementary pathologic review for a series of tumors in this patient is mandatory to confirm the origin of metastatic neck tumor, and to provide important guidance to best choose further chemotherapeutic regiments.

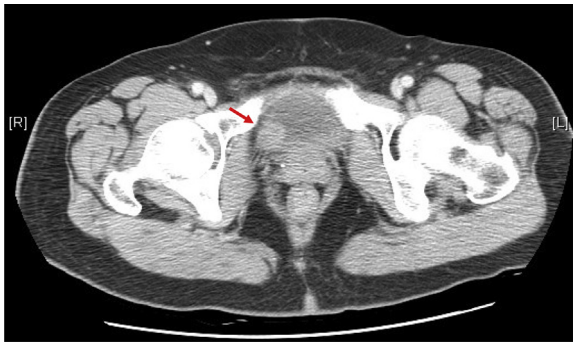


Fig. 1. A 2.6 × 2 cm tumor in the right posterior lateral wall of urinary bladder.

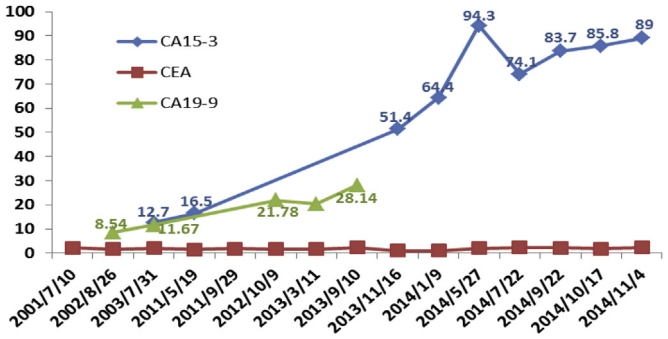


Fig. 2. Tumor marker follow-up data during disease course shown in Graph 1.

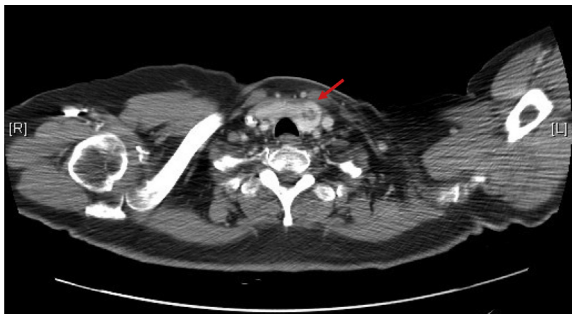
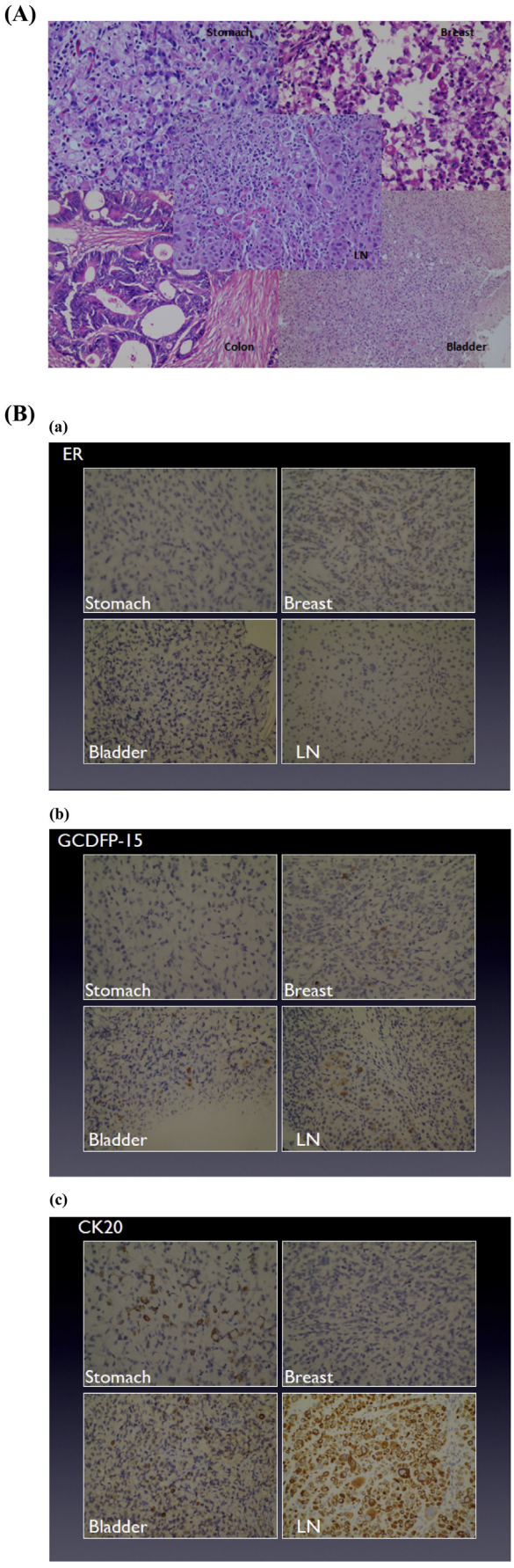


Fig. 3. Left supraclavicular lymph node lesion.

3. Pathologic finding

We reviewed specimens microscopically and immunohistochemically with a pathologist, and the urinary bladder lesion disclosed signet ring cell appearance (Fig. 1) with CK7 (+). We preliminarily determined that the cancer had originated from the stomach. However, in the following lymph node lesion, we compared samples of these recurrent lymph nodes with original gastric, breast and colon cancer tissue. Microscopically, lymph node tissue showed compact sheets and nests of carcinomatous cells displaying round nuclei, distinct nucleoli and pink cytoplasm without obvious ductal or glandular structure. IHC stain showed ER (6F11) (faint +), PR (1A6) (−), CDX2 (−), CK20 (+), CK7 (+) and HER-2-neu(polyclone): negative (1+) (shown in Fig. 4A). Tracing back previous pathologic reports from gastric, breast and colon cancer, gastric tissue disclosed signet ring cells and some poorly differentiated cells scattered microscopically. IHC stain showed ER (−), PR (−), Her2 (−), CK7 (+), CK20 (+, partial) and CDX2 (−) (shown in Fig. 1). The patient's breast tissue revealed poorly differentiated cells diffusely infiltrating into the fibrous stroma and



between the benign mammary glands. IHC stain showed ER (++, 100%), PR (++, 100%), HER-2-NEU (++, 100%), CK7 (+), CK20 (−) and CDX2 (−) (shown in Fig. 4B). IHC stains from breast, gastric, urinary bladder and lymph node tissue were summarized in Table 1. The colon cancer presented in cribriform appearance with moderately glandular differentiation. Morphologically, colon cancer as the originating site was initially excluded. Due to the ambiguous result comparing lymph node tissue with gastric and breast tissue, we checked further breast cancer-specific IHC stain – GCDFP-15 (gross cystic disease fluid protein-15), which showed a positive predicted value for breast cancer up to 99%.[6] In this case, GCDFP was both positive at breast and lymph node tissue. Furthermore, we traced back to the urinary bladder pathologic specimen, which also showed GCDFP-15(+). Thereafter, we overruled our previous conclusion based upon this new information. The lymph node and previous urinary bladder lesions were both favored to be of breast cancer origin. Clinically, CK7+/CK20+ can be observed in approximately 11% of breast cancer cases,[7] and the new evidence supported our final diagnosis.

4. Discussion

We herein have reported a case of a 67-year-old woman presenting with metastatic carcinoma harboring signet ring cell picture involving urinary bladder, and later suffered from progressive lymph node metastasis with underlying triple primary cancers including gastric, breast and colon cancer. The case reported met the MPN criteria mentioned above, and presented each tumor with the interval of more than 1 year, indicating that they were metachronous triple PMNs. Recurrent gastric cancer with bladder metastasis was diagnosed according to microscopic findings and IHC profiles expression. Later, due to multiple neck lymph nodes that progressed despite anti-cancer treatment, we arranged neck lymph node biopsy and subsequent complementary pathologic study adjusted our final diagnosis to recurrent breast cancer with eventual lymph node metastasis.

Over the past two decades, the incidence of second primary malignancy has progressively risen among cancer survivors and is an issue of increasingly greater concern in oncology. The increasing incidence may be due to the elevated rate of early cancer detection, improved cancer treatment and better supportive care with longer survivor life expectancy. The synchronous occurrence of multiple cancers, although rare, has been reported sporadically in the previous literature.[8–11] Our own data from a single Taiwan cancer center institute (Chang Gung Memorial Hospital, CGMH, Taoyung, Taiwan) showed that from 2002 to 2012, 1413 patients (0.64%) were diagnosed with triple primary cancers and 305 patients (0.13%) were diagnosed with multiple malignancies of more than 3 cancers. From our data, a total of 7825 patients were diagnosed with gastric cancer and 14,941 patients were diagnosed with breast cancer in the same period of time. Among those gastric cancer patients, 534 patients (6.8%) had second primary cancers, including 100 patients (1.28%) with colon cancer and 11 patients (0.14%) with breast cancer as a second primary neoplasm. Among breast cancer patients, 1437 patients (9.6%) had second primary cancer, including 52 patients (3.5%) with cervical cancer and 47 patients (3.1%) with colon cancer

Fig. 4. A. Microscopic appearance of three primary malignancies including stomach, breast and colon, compared with bladder and lymph node lesions. **B**. IHC stain for further differentiation In these 3 pictures, we compared ER, GCDFP-15 and cytokeratin 20 (CK20) manifestations in gastric, breast, bladder and lymph node tissues separately for clarification of recurrence tissue origin. (a) Both breast and lymph node tissues showed ER (+), but not gastric and bladder tissue. (b) Breast, lymph node and bladder tissues all disclosed breast cancer-specific marker, GCDFP-15, positive, except gastric cancer. (c) Both gastric, lymph node tissue and bladder tissue all revealed CD20 (+).

Table 1
Summary of IHC stain between gastric, breast, urinary bladder and lymph node tissues.

	ER	PR	Her2/neu	Mammoglobin	GCDFP-15	CK7	CK20	CDX2
Stomach	–	–	–	–	–	+ Moderate	+ Focal faint	–
Breast	2+ Faint	2+	2+	–	+ Focal faint	+ Strong	+ Focal faint	–
Urinary bladder	–	– Focal, <1%	2+ FISH (–)	–	+ Focal faint	+ Strong	+ Focal faint	–
LN	+ 2%, Faint	–	1+ 5%, Faint	–	+ Focal faint	+ Strong	+ Strong	–

as second primary neoplasm (unpublished data from CGMH cancer registry). Therefore, cases with triple primary malignancies are extremely rare. Therefore, the limited knowledge to be derived from such a rare experience contributes to the challenge upon clinical diagnosis despite detailed history-taking, physical examination, thorough imaging check-up and advanced immunohistochemical stain techniques. Yet knowledge gained from these rare cases, however limited, may aid in the diagnosis of future cases.

Clinically, we observed typically multicentric tumors involved with shared risk factor exposure and/or genetic predisposition with the phenomenon called “field cancerization”, especially in the head and neck area, and colorectal and urinary tract cancers. Conversely, the situation of multiple tumors involving diverse sites commonly has occurred by coincidence; however, it is also possible that field cancerization plays a role in their development. In addition, chemotherapy and radiotherapy may also contribute to the development of neoplasms, such as secondary leukemia and sarcoma.[12,13]

Hereditary cancer syndrome accounts for only 5% of all malignancies and usually presents with the following characteristics: 1) strong family history with high penetrance genotypes, such as hereditary breast and ovarian cancer syndrome with BRCA-1 gene and familial adenomatous polyposis with FAP gene; 2) multiple primary cancers with or without specific tissue type, such as Li-Fraumeni syndrome with early onset sarcoma, adrenocortical carcinoma, brain tumor, leukemia or premenopausal breast cancer; hereditary diffuse gastric cancer with diffuse gastric cancer and invasive lobular breast carcinoma; 3) unusual clinical presentation, such as early onset in hereditary diffuse gastric cancer, Lynch syndrome, and FAP (or multicentric tumors with Von Hippel-Lindau syndrome, heritable retinoblastoma, FAP); or 4) associated non-malignant disease, such as mucocutaneous pigmentation in Peutz-Jeghers syndrome or ataxia telangiectasia with cerebellar ataxia, telangiectasia, or vitiligo.[14–16]

In Taiwan, breast cancer is the most prevalent type of cancer for females, with up to 10% of the breast cancers associated with specific hereditary mutations in single-acting genes.[17] Hereditary breast cancer may be present with the following syndromes: hereditary breast and/or ovarian cancer syndrome (HBOC syndrome) linked to mutation in BRCA1 or BRCA2 gene; Li-Fraumeni syndrome with a germline TP53 gene mutation; and Cowden syndrome/PTEN hamartoma syndrome, an autosomal disorder associated with germline mutations in the PTEN tumor suppressor gene.[18–20] There are some additional genetic mutations associated with breast/ovarian cancer risk, such as CDH1 gene noted in hereditary diffuse gastric cancer syndrome, STK11/LKB1 gene shown in Peutz-Jeghers syndrome, and MMR (Mismatch repair) gene including MLH1, MSH2, MSH6 and PMS2 or EPCAM gene deletion expressed in Lynch syndrome.[21–23] According to the National Comprehensive Cancer Network (NCCN) guidelines, the criteria for which further genetic risk evaluation should be considered in breast cancer patients includes a known mutation in a breast cancer susceptibility gene within the family, early-age-onset breast cancer, triple negative (ER-, PR-, Her2-) breast cancer, two breast cancer primaries in a single individual, invasive ovarian cancer, male breast cancer, and breast cancer at any age with a) $\geq$ 1 close blood relative with breast cancer at $\leq$ 50 years of age; b) $\geq$ 1 close blood relative with ovarian cancer at any age; c) $\geq$ 2 close blood relative with breast cancer and/or pancreatic cancer at any age; d) combination of $\geq$1 of the following malignancies: pancreatic cancer, prostate cancer (Gleason score $\geqq$ 7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, thyroid cancer, kidney cancer, hamartomatous polyps of the gastrointestinal tract, and diffuse gastric cancer.[24]

Hereditary syndromes with increased risk for gastric cancer include: 1) hereditary diffuse gastric cancer, 2) Lynch syndrome/hereditary non-polyposis colorectal cancer, 3) juvenile polyposis syndrome, 4) Peutz-Jeghers syndrome and 5) familial adenomatous polyposis. Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant syndrome characterized by the development of diffuse (signet ring cell) gastric cancers at a young age.[25] Mutation of the CDH1 gene (the gene encoding the cell adhesion molecular E-cadherin) mutation noted in 30–50% of gastric cancer patients.[26] The lifetime cumulative risk in CDH1 mutation carriers to develop gastric cancer is estimated at 67% for men and 83% for women by the age of 80 years, and the risk of developing lobular breast cancer in women is up to 60% by age 80.[25,27] According to the NCCN guidelines, cases meeting any the following criteria should undergo further risk assessment and genetic evaluation: a) a known mutation in a gastric cancer susceptibility gene within the family, b) early-age-onset gastric cancer (<50 years of age), c) a diffuse gastric cancer occurring before age 40 years, d) personal or family history of diffuse gastric cancer and lobular gastric cancer, one diagnosed before age 50 years, e) two gastric cancer cases in family, one individual under age 50 years with confirmed diffuse gastric cancer, and f) three confirmed diffuse gastric cancer cases in first and second degree relatives independent of age.[24]

Syndromes linked to genetic susceptibility to colorectal cancer are: (1) familial adenomatous polyposis (FAP), (2) Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC), (3) MUTYH-associated polyposis, and then some less common syndromes such as Tuir-Torre, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, juvenile polyposis, and serrated polyposis syndromes. Colorectal cancer screening is recommended for those patients with a higher potential for inherited colon cancer.

Specific clinical features associated with different genetic mutations as well as familial history and other risk factors may provide hints for the diagnosis of hereditary cancers. In our case, the patient was diagnosed with gastric cancer, then left breast invasive lobular carcinoma and later proximal transverse colon cancer. Pathological review revealed that the urinary bladder was impressed as being gastric in origin with signet ring cell appearance morphologically; but later, a different pathological expression of lymph node lesions showed positive breast cancer-specific marker expression (GCDFP-15). As a result, breast cancer origin was favored. These findings

together with the patient's triple primary malignancy diagnosis, led to the suspicion of a hereditary syndrome.

Further genetic study for CDH1 gene, STK11/LKB1 gene, EPCAM gene deletion or MMR gene, including MLH1, MSH2, MSH6 and PMS2 are appropriate for evaluation of hereditary gastric cancer with breast cancer occurrence or STK11/LKB1 gene. Unfortunately, the patient expired before further evaluation could be performed, and we were not able to conduct genetic testing for a definitive confirmation. However, according to the patient's clinical course and disease behavior, diffuse gastric cancer, breast cancer and colorectal cancer were concluded to be the patient's functional disease combination.

Conflict of interest

No relationship to disclosure.

References

1. Curtis RE, Freedman DM, Ron E, et al. New Malignancies among Cancer Survivors: SEER Cancer Registries, 1973-2000. National Cancer Institute. NIH Publ. No. 05–5302, 2006 http://seer.cancer.gov/archive/publications/mpmono/MPMonograph_complete.pdf).
2. Warren S, Gates D. Multiple primary malignant tumors: a survey of the literature and a statistical study. *Am J Cancer*. 1932:1358–1414.
3. Schwartz LH, Ozsahin M, Zhang GN, et al. Synchronous and metachronous head and neck carcinomas. *Cancer*. 1933;74:1994.
4. Morris LG, Sikora AG, Patel SG, et al. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. *J Clin Oncol*. 2011;29:739–746.
5. Braakhuis BJ, Tabor MP, Leemans CR, et al. Second primary tumors and field cancerization in oral and oropharyngeal cancer: molecular techniques provide new insights and definitions. *Head Neck*. 2002;24:198–206.
6. Wick MR, Lillemoe TJ, Copland GT, et al. Gross cystic disease fluid protein-15 as a marker for breast cancer: immunohistochemical analysis of 690 human neoplasms and comparison with alpha-lactalbumin. *Hum Pathol*. 1989;20:281–287.
7. Lindner V, Gasser B, Debbiche A, et al. Ovarian metastasis of colorectal adenocarcinomas. A clinico-pathological study of 41 cases. *Ann Pathol*. 1999;19:492–498.
8. Iioka Y, Tsuchida A, Okubo K, et al. Metachronous triple cancers of the sigmoid colon, stomach, and esophagus: report of a case. *Surg Today*. 2000;30:368–371.
9. Tamura M, Shinagawa M, Funaki Y. Synchronous triple early cancers occurring in the stomach, colon and gallbladder. *Asian J Surg*. 2003;26:46–49.
10. Leong BD, Ramu P, Kumar VM, et al. Synchronous adenocarcinoma of caecum, transverse colon and jejunum. *Med J Malaysia*. 2008;63:148–149.
11. Chong VH, Idros A, Telisinghe PU, et al. Triple synchronous gastrointestinal malignancies: a rare occurrence. *Singapore Med J*. 2010;51:e176–e177.
12. Fianchi L, Pagano L, Piciocchi A. Characteristics and outcome of therapy-related myeloid neoplasms: report from the Italian network on secondary leukemias. *Am J Hematol*. 2015;90:E80–E85.
13. Hulegardh E, Nilsson C, Lazarevic V. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. *Am J Hematol*. 2015;90:208–214.
14. Rahner N, Steinke V. Hereditary cancer syndromes. *Dtsch Arztebl Int*. 2008;105:706–714.
15. Pharoah PD, Day NE, Daffy S. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer*. 1997;71:800–809.
16. Berliner JL, Fay AM. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2007;16:241–260.
17. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med*. 2008;359:2143–2153.
18. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. *Cell*. 2002;108:171–182.
19. Schneider Katherine. *Li-fraumeni Syndrome*. GeneReviews; 2013.
20. Pilarski R. Cowden syndrome: a critical review of the clinical literature. *J Genet Couns*. 2009;18:13–27.
21. Schrader KA, Masciari S, Boyd N, et al. Hereditary diffuse gastric cancer: association with lobular breast cancer. *Fam Cancer*. 2008;7:73–82.
22. Hemminki A, Markie D, Tomlinson I, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature*. 1998;391:184–187.
23. Peltomaki P, Vasen H. Mutations associated with HNPCC predisposition – update of ICG-HNPCC/INSiGHT mutation database. *Dis Markers*. 2004;20:269–276.
24. *Genetic/familial High-risk Assessment: Breast and Ovary. NCCN Guideline Version 1*. 2015.
25. Fitzgerald RC, Hardwick R. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet*. 2010;47:436e444.
26. Gayther SA, Gorringe KL, Ramus SJ, et al. Identification of germ-line E-cadherin mutations in gastric cancer families of European origin. *Cancer Res*. 1998;58:4086–4089.
27. Pharoah PD, Guilford P, Caldas C, et al. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology*. 2001;121:1348–1353.